Remarks

Claims 1, 5-9, 14, 20, 22-25, 27, 29, 35-39, 41, 42, 44-49, 51-53, 55-59, and 69-84 are pending.

Rejections Under 35 USC § 103

1. Claims 1, 5-9, 20, 22-25, 27, 35-39, 44, 45, 47-49, 51-53, 55, 56, 69-71, and 75 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033), and Landers et al. (U.S. Patent No. 6,703,228). Applicant respectfully traverses this rejection.

Lizardi discloses a method of rolling circle amplification (RCA) involving replication of single-stranded DNA molecules (see column 19, lines 21-23). Lizardi discloses use of a rolling circle replication primer of defined sequence that hybridizes to an amplification target circle (ATC) followed by rolling circle replication of the ATC primed by the rolling circle replication primer to produce a tandem sequence DNA (see column 19, lines 20-31). Lizardi fails to disclose or suggest non-circular degenerate primers, fails to disclose or suggest directly hybridization of a plurality of non-circular degenerate primers to each amplification target circle and fails to disclose or suggest directly formation of multiple tandem sequence DNA products by extension of said multiple primers.

Landers et al. discloses PCR methods of genotyping including degenerate oligonucleotide primed-PCR (DOP-PCR) and arbitrarily primed PCR (AP-PCR) (see column 15, line12 – column 16, line 26 and column 17, lines 28-29). DOP-PCR as well as AP-PCR are used to first produce reduced complexity genomes that can then be utilized in a genotyping analysis (see column 4, lines 12-19). To accomplish this purpose, the primers of Landers et al. are designed to replicate on a subset or portion of genomic sequences present in a sample.

Claims 1, 5-9, 20, 22-25, 27, 35-39, 44, 45, 47-49, 51-53, 55, 56, 69-71, and 75 are drawn to a process for selectively amplifying nucleic acid sequences. The process involves contacting multiple single stranded non-circular degenerate oligonucleotide primers (P1) and one or more single stranded amplification target circles, where each ATC hybridizes to a plurality of the P1 primers, under conditions that promote rolling circle replication of the amplification target circle

by extension of the P1 primers to form multiple tandem sequence DNA (TS-DNA) products. Thus the claims require amplification of a nucleic acid sequence that involves the use of single stranded amplification target circles, hybridization of a plurality of P1 primers of degenerate sequence to each ATC under conditions that promote rolling circle replication of the ATC by extension of the P1 primers to form multiple TS-DNA products by extension of the P1 primers. As such, the amplification of the nucleic acid sequence is a product of rolling circle amplification primed at different sites on the template ATC and results in multiple TS-DNA products by extension of the P1 primers.

In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *See In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988); *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987). In order for a reference to be effective prior art under 35 U.S.C. § 103, it must provide a motivation whereby one of ordinary skill in the art would be led to do that which the applicant has done. *See Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). The Patent Office has the burden under § 103 to establish a *prima facie* case of obviousness, which can be satisfied only by showing some objective teaching in the prior art would lead one to combine the relevant teachings of the references. *See In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988).

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is

not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted)

The Office Action alleges, in part, at page 4, lines 12-19, that Lizardi teaches a method of amplification comprising contacting multiple single stranded non-circular random oligonucleotide primers (P1), one or more single stranded amplification target circles (ATCs) under conditions where each ATC hybridizes to a plurality of said P1 primer, wherein said conditions promote rolling circle replication of said ATC by extension of the P1 primers to form multiple tandem sequence DNA (TS-DNA) products. The Office Action admits that Lizardi does not teach degenerate primers (See Office Action page 7, line 14).

In support of its interpretation of Lizardi, the Office Action (page 5 and page 7) cites column 25, lines 36-57 as well as column 28, lines 8-18 of Lizardi, which describe strand displacement cascade amplification (SDCA). The Office Action alleges that SDCA teaches the use of multiple primers hybridizing to and priming rolling circle replication of an ATC. This is not the case. SDCA begins with rolling circle replication of an ATC primed by a single rolling circle replication primer to form TS-DNA. Secondary strand displacement is accomplished by hybridizing secondary DNA strand displacement primers to TS-DNA (See Lizardi column 25, lines 24-28). Secondary DNA strand displacement primers do not bind to the ATC. Secondary DNA strand displacement primers hybridize to, and prime replication of, TS-DNA to form what is termed TS-DNA-2. In other words, secondary DNA strand displacement primers bind to a copy of (the complement of) the ATC, not to the ATC itself. The secondary DNA strand displacement primers have sequence matching (analogous to) part of the OCP or ATC used to generate TS-DNA (See column 12, lines 21-29), therefore, by definition, they do not bind to the ATC (See Lizardi column 25, lines 43-45). Once the TS-DNA-2 is generated, tertiary DNA strand displacement primers can then hybridize to, and prime replication of the TS-DNA-2 generated from the replication of the initial TS-DNA, primed by the secondary DNA strand displacement primers to form TS-DNA-3 (See Lizardi, column 27, lines 2-4).

While it is true that the methods of Lizardi generically encompass the use of multiple primers and that in some embodiments of the methods of Lizardi the use of rolling circle

replication primers and tertiary DNA strand displacement primers together might result in more than one primer hybridizing to a single amplification target circle, Lizardi does not specifically disclose and certainly does not suggest the use of multiple rolling circle replication primers nor formation of multiple tandem sequence DNA products from multiple primings of a single amplification target circle. It is clear that the mere fact that certain subject matter is disclosed within a broader generic disclosure does not make obvious the specific subject matter not specifically disclosed. In re Baird, 16 F.3d 380, 382, 29 USPQ2d 1550 (Fed. Cir. 1994). In the case of an obviousness rejection, an inherent but obscure feature of a reference cannot provide the suggestion or motivation to use such a feature in combination with other references. The cited references must suggest what is claimed, not merely inherently disclose disparate elements of the claimed invention, which is all that the present rejection provides. Neither Lizardi nor Landers et al. provide any disclosure or suggestion regarding rolling circle replication involving multiple primings of a single ATC and thus do not provide any suggestion to focus the method of Lizardi on the claimed use of multiple primers and multiple primings of a single ATC.

Aside from the fact that neither Lizardi nor Landers et al. provide any disclosure or suggestion regarding the use of multiple rolling circle replication primers nor formation of multiple tandem sequence DNA products from multiple primings of a single amplification target circle, the present claims also require the use of degenerate primers for priming rolling circle replication of single stranded amplification target circles. As previously discussed, degenerate primers are defined in the current specification on page 6, lines 11-22 where the specification provides "Degenerate refers to an oligonucleotide in which one or more of the nucleotide positions is occupied by more than one base, i.e., a mixture of oligonucleotides of defined length in which one or more positions of an individual member of the mixture is occupied by a base selected at random from among more than one possibilities for that position." The Office Action admits on page 7, line 14 that Lizardi fails to teach degenerate primers. The Office Action relies on Landers et al. for allegedly teaching the missing element of Lizardi, namely that of degenerate primers (see Office Action page 7, lines 15-17). The Office Action further alleges (page 8, lines 1-4) that it would have been *prima facie* obvious to one of ordinary skill in the art to have included

degenerate primers of Landers et al. in the method of Lizardi. The Office Action argues (page 8, lines 2-4) that those of skill in the art would have been motivated to do so because Landers et al. allegedly provides that degenerate primers allow amplification of unknown DNA sequences. Applicants disagree that it would have been obvious to use the primers of Landers et al. in the method of Lizardi.

Applicants submit that one of skill in the art would not be motivated to combine the primers taught by Landers et al. with the methods taught by Lizardi because (1) the problem to be solved by the claimed methods are not the same problem to be solved by Landers et al.; (2) the methods cited by the Office Action are specifically directed to an unrelated method of amplification than Lizardi and the claimed methods; and (3) the methods cited by the Office Action do not use degenerate primers to amplify a circular DNA template.

First, Applicants direct the Examiner's attention to a problem to be solved of the current application and the methods employed to solve the problem. Page 5, lines 18-21 of the instant specification provides "A further advantage of the method of the present invention is that, as an RCA reaction, it selectively amplifies circular DNA target molecules without the need for "subsetting", or reducing the complexity of the DNA target" (emphasis added). In other words, a problem with previous methods was the need to reduce the complexity of the DNA target, a problem the claimed method solved. In addition, the statement above, as well as the claims, indicate that the method of amplification is rolling circle amplification (RCA) as opposed to polymerase chain reactions (PCR), ligase chain reactions (LCR), self-sustained sequence replication (3SR), nucleic acid based amplification (NASBA), strand displacement amplification (SDA) and amplification with Qβ replicase (see page 1, lines 21-28 of the instant specification). Furthermore, the claimed methods can be carried out isothermally (see specification page 3, lines 10-13).

As discussed above, the currently claimed methods solve the problem of amplifying a circular DNA molecule without having to reduce the complexity of the DNA target (see again page 5, lines 18-21 of the instant specification). The portions of Landers et al. cited in the Office Action (specifically column 17, lines 28-42 and 60-64 as well as column 4, lines 12-29) disclose

the generation of what they term reduced complexity genomes or RCGs. In particular, Landers et al. teaches methods of genotyping SNPs (single nucleotide polymorphisms) in a genome using reduced complexity genomes. In other words, in order for the method of Landers et al. to work, you must first reduce the complexity of the genome sought to be genotyped. This is precisely contrary to the claimed methods. The claimed methods allow for selective amplification of nucleic acid sequences without the need to reduce the complexity of the target. There is no need to reduce the complexity of the amplification target circles of the claimed method (or of the method of Lizardi) because they already have much less sequence complexity than the genomes of Landers et al. There is nothing in the cited portions of Landers et al. that would suggest that the primers of Landers et al. would be useful in the method of Lizardi. Although Landers et al. mentions that the primers of Landers et al. can be designed without knowledge of the sequence of the target nucleic acids, this is not the same as suggesting that primers having sequences not based on a target sequence would or could be useful in amplifying the amplification target circles of Lizardi, which have limited sequence complexity.[1] Further, there is no reason present in the cited portions of either Lizardi or Landers et al. that suggests why or how primers designed without knowledge of the sequence of an amplification target circle of Lizardi would be useful or provide any benefit to the method of Lizardi. Thus, the alleged reason provided in the rejection for using the primers of Landers et al. in the method Lizardi does not apply to the method of Lizardi. As such, one of skill in the art would not be motivated to take components out of the methods of Landers et al. to combine them with Lizardi to achieve the claimed methods because the problems to be solved by Landers et al are unrelated and are furthermore contrary to the problem solved by the instant claims.

Furthermore, the only disclosure of using the alleged degenerate primers disclosed in Landers et al. is specifically for the purpose of generating RCGs. Column 4, lines 12-29 cited by the Office Action illustrate this fact. Column 4, lines 12-29 of Landers et al. describe DOP-PCR.

[1] The primers of Landers et al. designed without knowledge of the target sequence work in the method of Landers et al. because genomes have a high sequence complexity and are thus essentially certain to include sequences complementary to any of the primers of Landers et al. that have arbitrarily chosen sequences. This is not the case with the amplification target circles of Lizardi, which have a low sequence complexity.

DOP-PCR is a method of generating RCGs using what the Office Action relies on as degenerate primers, thus the name degenerate oligonucleotide priming PCR (DOP-PCR). The RCGs generated by DOP-PCR are then used for further genotyping analysis. The name itself also gives rise to support that one of skill in the art would not be motivated to combine the degenerate primers of Landers et al. with the methods of Lizardi to achieve the claimed invention. As discussed above, Lizardi teaches methods involving rolling circle amplification. Suffice it to say, that rolling circle replication is not the same as PCR. Landers et al. only discloses the use of their "degenerate primers" in PCR reactions. Nowhere in Landers et al. is there any discussion, motivation, or suggestion to use their primers in anything other than a PCR reaction. While Applicants recognize that a teaching, motivation or suggestion to combine need not be explicit in a cited reference, Applicants submit that due to the differences in rolling circle replication and PCR, expressly the fact that rolling circle replication can be carried out isothermally, one of skill in the art would not be motivated to combine the primers disclosed in Landers et al. with the methods of Lizardi.

The Office Action appears to appreciate this point by citing column 17, lines 28-42 and 60-64 for allegedly teaching amplification of genomic double-stranded DNA circles (YACs) with multiple degenerate primers. As described above, degenerate primers are defined as an oligonucleotide in which one or more of the nucleotide positions is occupied by more than one base, i.e., a mixture of oligonucleotides of defined length in which one or more positions of an individual member of the mixture is occupied by a base selected at random from among more than one possibility for that position. In other words, each degenerate nucleotide position is occupied, at random, with a base. The result is that each of the present primers has at least a portion that has a sequence that is random relative to the other primers and each primer can be generated without knowledge of the target sequence to which it will bind. The Office Action cites column 17, lines 28-42 and 60-64, of Landers et al. which describes a method for generating a reduced complexity genome (RCG) referred to as arbitrarily primed PCR (AP-PCR). The Office Action incorrectly equates the arbitrary primers of Landers et al. to the claimed degenerate primers. The arbitrary primers of Landers et al. are not degenerate. While the AP-PCR primers of Landers et al. have

sequence that is arbitrarily chosen, the primers have a single, specific, non-random sequence. As Landers et al. notes, the primers used in AP-PCR are similar to the DOP-PCR primers with the exception that the AP-PCR primers consist only of the arbitrarily-selected nucleotides and not the 5' flanking degenerate residues or the tag present in primers for DOP-PCR (see column 17, lines 35-39). The arbitrarily-selected nucleotides of the AP-PCR primers are equivalent to the "TARGET" nucleotide sequence of the DOP-PCR primers. As Landers et al. notes (column 15, lines 18-20), the "'TARGET' nucleotide sequence includes at least 5 arbitrarily selected nucleotide residues that are the same for each primer of the set" (emphasis added). The fact that the primers are specifically designed such that nucleotide residues in each of the primers of the primer set are the same excludes them from being degenerate primers as defined in the present application. Thus, the AP-PCR primers of Landers et al. are not degenerate and accordingly are not the same as the claimed primers. Accordingly, Landers et al. cannot cure the deficiency in Lizardi.

Furthermore, Applicants again point out that the methods disclosed in the cited portion of Landers et al. are directed to DOP-PCR and arbitrarily primed PCR (AP-PCR). AP-PCR utilizes short oligonucleotides as PCR primers to amplify a discrete subset of portions of a high complexity genome (see column 17, lines 28-31). The AP-PCR method is similar to DOP-PCR with the exception that AP-PCR does not use degenerate primers. As such, Applicants submit that the AP-PCR method is irrelevant to the claimed method. Applicant reminds the Examiner that the claimed methods require degenerate primers and not arbitrary or random primers. Furthermore, Applicants submit the methods taught in column 17 of Landers et al. are PCR methods and not rolling circle replication, despite the fact that the target is a circle. Again, Applicants submit that due to the differences in rolling circle replication and PCR, expressly the fact that rolling circle replication can be carried out isothermally, one of skill in the art would not be motivated to combine the primers disclosed in Landers et al. with the methods of Lizardi.

Because the problem to be solved by Landers et al. through the use of the alleged degenerate primers is specifically drawn to the reduction of complex genomes, a step and problem specifically overcome by the instant claims, one of skill in the art, because such a step is

not required in the claimed methods, would not be motivated to combine Landers et al. with the methods of Lizardi. For this reason and all the reasons stated above, Applicants submit that one of skill in the art would not be motivated to combine the primers disclosed in Landers et al. with the methods of Lizardi. As such, Lizardi and Landers et al., either alone or in combination, fail to make obvious claims 1, 5-9, 20, 22-25, 27, 35-39, 44, 45, 47-49, 51-53, 55, 56, 69-71, and 75. As such, Applicant respectfully requests withdrawal of this rejection.

2. Claims 14, 57, and 58 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033), and Landers et al. (U.S. Patent No. 6,703,228) in further view of Navarro et al. (J. Virol. Meth., vol. 56, pp. 59-66, 1996). Applicant respectfully traverses this rejection.

Claims 14, 57, and 58 depend from claim 1 and therefore encompass all the limitations of claim 1. Applicant notes that the rejection applies Lizardi and Landers et al. in the same way and for the same disclosure for which Lizardi and Landers et al. were applied in the rejection of claims 1, 5-9, 20, 22-25, 27, 35-39, 44, 45, 47-49, 51-53, 55, 56, 69-71, and 75 under 35 U.S.C. § 103(a) discussed above. As discussed above, Lizardi and Landers et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of degenerate sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication. Navarro et al. fails to supplement this gap in Lizardi and Landers et al.

Navarro et al., which was cited for allegedly teaching amplification of circular viriods using multiple random hexamers and AMV reverse transcriptase, fails to cure the deficiencies in Lizardi and Landers et al. discussed above.

The Office Action also cites, on page 8, lines 11-13, Figure 1 of Navarro et al as well as page 59, first paragraph; page 60, paragraphs 4 and 5 and page 61, first paragraph of Navarro et al. for allegedly teaching amplification of circular viriods using multiple random hexamers and AMV reverse transcriptase. The Office Action implies (and the rejection relies on the assumption that) Navarro et al. involves rolling circle amplification of a circular template using

random primers as rolling circle replication primers. Navarro et al. does not disclose or suggest rolling circle amplification of a circular template and does not disclose or suggest amplification via degenerate primers. The method of Navarro et al. involves reverse transcription of a circular RNA molecule via sequential first strand and second strand synthesis followed by PCR amplification of the resulting linear, double-stranded cDNA (see Section 2.2 bridging pages 60 and 61 and Figure 1). This is not rolling circle amplification and the method does not use degenerate primers for amplification. Rather, the method of Navarro et al. uses random primers merely to produce cDNA by reverse transcription which is then amplified via conventional PCR of the linear, double-stranded cDNA. There is no nexus between the method of Navarro et al. and the methods of Lizardi and Landers et al. For at least these reasons, Navarro et al. does not correct the deficiencies in the disclosures of Lizardi and Landers et al.

For all of the above reasons, Lizardi, Landers et al., and Navarro et al., either alone or in combination, fail to make obvious claims 14, 57, and 58. As such, Applicant respectfully requests withdrawal of this rejection.

3. Claims 29, 41, 46, and 47 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033), and Landers et al. (U.S. Patent No. 6,703,228) in further view of Eckstein et al. (Trends in Bioch. Sci., vol. 14(3), PP. 97-100, 1989). Applicant respectfully traverses this rejection.

Claims 29, 41, 46, and 47 depend from claim 1 and therefore encompass all the limitations of claim 1. Applicant notes that the rejection applies Lizardi and Landers et al. in the same way and for the same disclosure for which Lizardi and Landers et al. were applied in the rejection of claims 1, 5-9, 20, 22-25, 27, 35-39, 44, 45, 47-49, 51-53, 55, 56, 69-71, and 75 under 35 U.S.C. § 103(a) discussed above. As discussed above, Lizardi and Landers et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of degenerate sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication.

Eckstein et al., which was cited for disclosing modified nucleotides, was not cited for and fails to cure the deficiencies in Lizardi and Landers et al. discussed above. The cited portions of Eckstein et al. do not supply what is missing from Lizardi and Landers et al. Thus, Lizardi, Landers et al., and Eckstein et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of degenerate sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication. Accordingly, Lizardi, Landers et al., and Eckstein et al.fail to make obvious claims 29, 41, 46, and 47. Applicant respectfully requests withdrawal of this rejection.

4. Claims 42 and 59 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033), Landers et al. (U.S. Patent No. 6,703,228), and in further view of Skerra (Nucleic Acids Research, Vol. 20, pp. 3551-3554, 1992). Applicant respectfully traverses this rejection.

Claims 42 and 59 depend from claim 1 and therefore encompass all the limitations of claim 1. Applicant notes that the rejection applies Lizardi and Landers et al. in the same way and for the same disclosure for which Lizardi and Landers et al. were applied in the rejection of claims 1, 5-9, 20, 22-25, 27, 35-39, 44, 45, 47-49, 51-53, 55, 56, 69-71, and 75 under 35 U.S.C. § 103(a) discussed above. As discussed above, Lizardi and Landers et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of degenerate sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication.

Skerra et al. was cited for disclosure of incorporation of a phosphorothioate nucleotide at the 3'-end of the primer renders it inactive to the 3'->5' exonuclease activity of DNA polymerases such as Vent and Pfu and use of a mixture of exonuclease-sensitive and exonuclease-resistant primers in the amplification reaction. This does not supply what is missing from Lizardi and Landers et al. Thus, Lizardi, Landers et al. and Skeera et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of degenerate

sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication. Accordingly, Lizardi, Landers et al. and Skeera et al. fail to make obvious claims 42 and 59. Applicant respectfully requests withdrawal of this rejection.

5. Claims 72 and 73 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033), Landers et al. (U.S. Patent No. 6,703,228), and in further view of Waggoner et al. (U.S. Patent No. 5,268,486). Applicant respectfully traverses this rejection.

Claims 72 and 73 depend from claim 1 and therefore encompass all the limitations of claim 1. Applicant notes that the rejection applies Lizardi and Landers et al. in the same way and for the same disclosure for which Lizardi and Landers et al. were applied in the rejection of claims 1, 5-9, 20, 22-25, 27, 35-39, 44, 45, 47-49, 51-53, 55, 56, 69-71, and 75 under 35 U.S.C. § 103(a) discussed above. As discussed above, Lizardi and Landers et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of degenerate sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication.

Waggoner et al. was cited for its disclosure of cyanine fluorescent dyes. This does not supply what is missing from Lizardi and Landers et al. Thus, Lizardi, Landers et al. and Waggoner et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of degenerate sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication. Accordingly, Lizardi, Landers et al. and Waggoner et al. fail to make obvious claims 72 and 73. Applicant respectfully requests withdrawal of this rejection.

6. Claim 83 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi (U.S. Patent No. 5,854,033), Landers et al. (U.S. Patent No. 6,703,228), and in further view of

Tuma et al. (Anal. Biochem., vol. 268, pp. 278-288, 1999). Applicant respectfully traverses this rejection.

Claim 83 depends from claim 1 and therefore encompasses all the limitations of claim 1. Applicant notes that the rejection applies Lizardi and Landers et al. in the same way and for the same disclosure for which Lizardi and Landers et al. were applied in the rejection of claims 1, 5-9, 20, 22-25, 27, 35-39, 44, 45, 47-49, 51-53, 55, 56, 69-71, and 75 under 35 U.S.C. § 103(a) discussed above. As discussed above, Lizardi and Landers et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of degenerate sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication.

Tuma et al. was cited for its disclosure of detecting single-stranded DNA and RNA and double-stranded DNA using intercalating dye SYBR gold. This does not supply what is missing from Lizardi and Landers et al. Thus, Lizardi, Landers et al. and Tuma et al., either alone or in combination, fail to disclose, suggest, or provide motivation for the use of primers of degenerate sequence in the method of Lizardi or hybridization of each amplification target circle to a plurality of primers such that multiple tandem sequence DNA products be produced by extension of the primers in rolling circle replication. Accordingly, Lizardi, Landers et al. and Tuma et al. fail to make obvious claim 83. Applicant respectfully requests withdrawal of this rejection.

Pursuant to the above remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A credit card payment via EFS WEB in the amount of $525.00, representing $525.00 for the Extension of Time fee for a small entity under 37 C.F.R. § 1.17(a)(3) and a Request for Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,
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Scott D. Marty, Ph.D.

12-27-07
Date